Use of Recombinant Factor VIIa in US Military Casualties for a Five-Year Period

Charles E. Wade, PhD, Brian J. Eastridge, MD, John A. Jones, BS, Susan A. West, RN, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Michael A. Dubick, PhD, Lorne H. Blackbourne, MD, and John B. Holcomb, MD

Background: Two prospective randomized trauma trials have shown recombinant factor VIIa (rFVIIa) to be safe and to decrease transfusion requirements. rFVIIa is presently used in 22% of massively transfused civilian trauma patients. The US Military has used rFVIIa in combat trauma patients for five years, and two small studies of massively transfused patients described an association with improved outcomes. This study was undertaken to assess how deployed physicians are using rFVIIa and its impact on casualty outcomes.

Methods: US combat casualties (n = 2,050) receiving any blood transfusion from 2003 to 2009 were reviewed to compare patients receiving rFVIIa (n = 506) with those who did not (n = 1,544). Propensity-score matching (primary analysis) and multivariable logistic regression were used to compare outcomes. Differences were determined at $p < 0.05$.

Results: Twenty-five percent of patients received rFVIIa. Significant differences were noted between groups in indices of injury severity (Injury Severity Score, Abbreviated Injury Scale score, and Glasgow Coma Scale score), admission physiology (systolic blood pressure, diastolic blood pressure, heart rate, temperature, base deficit, hemoglobin, and international normalization ratio), and use of blood products, indicating that patients treated with rFVIIa were more severely injured, in shock, and coagulopathic. For propensity-score matching, factors associated with death were used: Injury Severity Score, Glasgow Coma Scale score, heart rate, systolic blood pressure, diastolic blood pressure, Hgb, and total packed red blood cell. A total of 266 patients per group were matched; 52% of the rFVIIa group. After pairing, there were no significant differences in any of the demographics, including incidence of massive transfusion (53% vs. 51%). There was no difference in the rate of complications (21% vs. 21%) or mortality (14% vs. 20%) for patients not treated or receiving rFVIIa, respectively.

Conclusion: In military casualties, rFVIIa is used in the most severely injured patients based on physician selection rather than on guideline criteria. Use of rFVIIa is not associated with an improvement in survival or an increase in complications. The undetected bias of physician selection of patients for treatment with rFVIIa, likely, has an impact on case matching to achieve equivalence similar to that of randomized control studies. This inability to match populations, thus, prevents definitive interpretation of this study and others studies of similar design. This problem emphasizes the need to develop entry criteria to identify patients who could potentially benefit from use of rFVIIa and the need to subsequently perform efficacy studies.

Key Words: Mortality, Complications, Transfusion, Admission physiology, Coagulopathy.

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A predominant cause of potentially preventable deaths of military and civilian casualties is hemorrhage. It is the reported cause of death in >80% of combat casualties both before and after admission to a medical treatment facility.[1,2] For civilian patients, the in-hospital mortality rate caused by hemorrhage is 26% to 39%.[3,4] These military and civilian patients die predominantly of noncompressible uncontrolled hemorrhage attributed to injuries to the thorax or abdomen.[5,6] In addition, many of these patients have concomitant coagulopathy. Rates of coagulopathy at admission for military and civilian patients are 38% and 25% to 28%, respectively.[7–9] In the presence of uncontrolled bleeding and coagulopathy, damage control resuscitation (DCR) has been advocated.[10–12] Major tenets of this clinical practice guideline are early control of bleeding and correction of coagulopathy.

One portion of the US military DCR guidelines advocates consideration of the use of recombinant factor VIIa (rFVIIa) to address early coagulopathy and decrease death from hemorrhage. Similar guidelines were promulgated by civilian care providers.[13,14] More than 75% of the US Level I trauma centers recommended the use of rFVIIa in their massive transfusion protocols[15,16] based on an early randomized control trial demonstrating a decrease in blood requirements in patients with blunt injuries and an absence of major adverse events.[17] The early finding of a decrease in blood transfusions was recently confirmed in another randomized control trial (Hauser et al., submitted for publication). The US military also recommended the use of rFVIIa in patients requiring a massive transfusion because, early in the present conflicts, the full complement of blood components was not available, which required the use of alternative hemostatic strategies.[18,19] In the following years, a number of studies were undertaken on the efficacy and safety of rFVIIa in the care of the patients with traumatic injuries. However, no study was definitive as to the efficacy of rFVIIa in this

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From the Center for Translational Injury Research and Department of Surgery (C.E.W., J.B.H.), University of Texas Health Science Center, Houston, Texas; US Army Institute for Surgical Research (B.J.E., L.H.B., C.E.W., J.A.J., S.A.W., P.C.S.), Fort Sam Houston, Texas; Department of Hematology (J.G.P.), Walter Reed Army Medical Center, Bethesda, Maryland; and Departments of Pediatrics and Surgery (P.C.S.), University of Connecticut, Hartford, Connecticut.
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Address for reprints: Charles E. Wade, PhD, Center for Translational Injury Research and Department of Surgery, University of Texas - Health, 6431 Fannin, MSB 5.206, Houston, TX 77030; email: Charles.E.Wade@uth.tmc.edu.

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Wade C. E., Eastridge B. J., Jones J. A., West S. A., Spinella P. C., Perkins J. G., Dubick M. A., Blackbourne L. H., Holcomb J. B.,

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population, nor was an increase in complications demonstrated.[20–22] In studies of patients with combat-related injuries, a decrease in packed red blood cell (PRBC) requirements was noted in massively transfused patients who received rFVIIa early in the course of their resuscitation.[23] In a follow-on study of a similar patient population, a decrease in mortality was suggested with the early use of rFVIIa, with no increased risk of thrombotic events reported.[24] For these reasons, the military and some civilian centers have continued to provide access to rFVIIa for use in patients with hemorrhagic shock and anticipated to require a massive transfusion or have bleeding refractory to standard treatment.

Starting in 2006, we began systematic monitoring of blood component use in the treatment of US military casualties through the Joint Theater Trauma Registry (JTTR).[6,9,25] Use of rFVIIa as part of DCR was tracked. The purpose of this study was to assess in which military casualties rFVIIa was used in relation to the promulgated clinical practice guideline and the effectiveness and complication rates of its use.

PATIENTS AND METHODS

The JTTR collects data on patients treated in US military care facilities during the overseas contingency operations.[26] Part of the registry includes data on US military personnel with traumatic injuries who received transfusions of blood products from October 2003 to June 2009. Data from October 2003 to July 2006 were collected retrospectively from medical records and prospectively from then on. Use of rFVIIa was recorded, but the data are limited because factors such as time of administration and dose of rFVIIa were not entered. Physiologic characteristics at admission (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], temperature, base deficit, hemoglobin [Hgb] concentration, and international normalization ratio), indices of injury severity (Injury Severity Score [ISS], Abbreviated Injury Scale score, and Glasgow Coma Scale [GCS] score), use of blood products and fluids, complications, and time of death are available. For the use of PRBCs, one unit of fresh whole blood was counted as a unit of PRBC.[5] If outcome or time of death was not known or the patient died within 17 minutes of admission, the patient was excluded. The exclusion criteria were based on the first death noted to have received rFVIIa, thus limiting survival bias.[27] Data access was approved by the institutional review board at Brooke Army Medical Center.

The clinical practice guideline approved in theaters of combat suggests that rFVIIa use should be considered for administration to trauma patients or patients in shock who have major signs of hemorrhage based on established criteria (Table 1; http://www.usaisr.amedd.army.mil/cpgs.html) It is clearly stated in the guideline and reiterated by those in command that the criteria are guidelines only and not substitutes for clinical judgment. To assess adherence to the guidelines, a comparison was made between patients who received and did not receive rFVIIa, taking into consideration the criteria for use.

Complications were determined by notation in the patient record and codes of the *International Statistical Classification of Diseases and Related Health Problems, 9th ed*. Complications specifically associated with thromboembolic and other adverse events were recorded. These include pulmonary embolism, deep vein thrombosis, stroke, myocardial infarction, acute respiratory distress syndrome, and renal failure.

TABLE 1. Criteria for the Use of rFVIIa in the Military Clinical Practice Guidelines

a. Hypotensive from blood loss
b. Base deficit >6 mmol/L
c. Difficult to control bleeding associated with hypothermia (temperature <96°C)
d. Coagulopathic bleeding (clinically or INR >1.5)
e. Require damage control maneuvers
f. Require fresh whole blood
g. Anticipated or actual transfusion of >4 units of PRBC
h. Anticipated significant operative hemorrhage

Statistical Analysis

Admission characteristics, transfusion of blood products, and outcomes were compared between patients treated with rFVIIa and those who did not receive the drug. Data were analyzed for normality using a Kolmogorov-Smirnov test. Student's *t* test or Mann-Whitney *U* test was used to compare differences, as appropriate. Continuous data are presented as median (interquartile range). For dichotomous data, χ^2 or Fisher's exact test was used, as appropriate, to compare between groups. Kaplan-Meier log-rank test was used to compare unadjusted overall survival. Statistical significance was set at a $p < 0.05$ for all group comparisons, and specific p values are presented in the text.

In a second analysis, a multivariate survival analysis was conducted of all patients included in the study, and adjustments made for known confounders. A univariate logistic regression of admission variables and rFVIIa treatment was performed with mortality as the dependent variable. Variables with $p < 0.20$ on univariate analysis were included in the final model, where a multivariate logistic regression model was used to examine overall mortality. The logistic regression model was assessed using the area under the receiver operating characteristic (ROC) curve.

We calculated the propensity for treatment with rFVIIa on the basis of variables associated with mortality available for inclusion of the largest number of subjects. We matched each patient in the rFVIIa group to a patient who did not receive the drug and who had the closest propensity score using a standard greedy-matching algorithm.

RESULTS

Between October 2003 and June 2009, a total of 18,638 trauma records for US military casualties were entered into the JTTR. There were 2,101 (11.3%) patients who received at least 1 unit of blood. There were 5 (1%) patients who received rFVIIa and 46 (3%) who did not that met the exclusion criteria. Thus, the final number of patients studied was 2,050. There were 506 (25%) patients who received rFVIIa and 1,544 who did not. Review of the criteria for use of rFVIIa showed a significantly greater incidence of positive criteria in those patients receiving treatment (Table 2). However, there were still a significant

TABLE 2. Incidence of Criteria for the Use of Administration of rFVII

Criteria	No rFVIIa (n = 1,544)	rFVIIa (n = 506)
SBP <90 mm Hg	16 (1,387)	27* (457)
BD >6 mmol/L	27 (888)	49* (339)
Hypothermia <96°C	11 (857)	11 (264)
INR >1.5	30 (883)	48* (333)
Hgb <12 g/dL	47 (1,164)	56* (410)
Massive transfusion (%)	27 (1,544)	66† (506)
ISS >15 (%)	54 (1,544)	82† (506)

Significantly different at * $p < 0.005$ and at † $p < 0.0001$.
Number of patients for whom the data were available is shown in parentheses.

number of patients (>69%) who met one or more criteria for use and did not receive rFVIIa. This lack of treatment based on guideline criteria suggests that either clinician judgment was used with the preference being independent of guideline criteria or rFVIIa was unavailable.

Patients who received rFVIIa were more severely injured than those who did not receive it. There was a greater incidence of ISS >15 (82% vs. 54%, $p < 0.0001$) and of the need for a massive transfusion (≥10 units of PRBC in 24 hours; 66% vs. 27%, $p < 0.0001$). Treated patients also had a greater incidence of severe injury (Abbreviated Injury Scale score ≥3) to the thorax, abdomen, and head (Table 3). There was a similar incidence of patients with an ISS of 75 (1.1% vs. 1.0%). The majority of physiologic variables were significantly different between populations at admission (Table 4). Subsequently, those patients treated with rFVIIa required more blood components (Table 5). The rate of complications (26% vs. 15%, $p < 0.0001$) increased with the use of rFVIIa as would be expected for a more severely injured population (Table 6). Overall mortality was greater in those patients receiving rFVIIa (24% vs. 12%, $p < 0.0001$), whereas the median time to death occurred later (409 [160–7817] minutes vs. 172 [60–2880] minutes, $p < 0.0001$; Table 7). Patients who were not treated had a greater percentage of deaths (73%, 131 of 180) that occurred in the first 24 hours compared with 58% (69 of 119; $p < 0.03$) of patients who were treated with rFVIIa.

Admission vital signs and laboratory values, ISS, GCS score, use of blood components, and use of rFVIIa were significantly different between patients who lived and died. A univariate regression analysis was performed for association with mortality using all significant variables. On multivariate logistic

TABLE 3. Percentage of AIS ≥ 3 for Various Body Regions for Patients Who Were Not Treated and Treated With rFVIIa

Body Region	No rFVIIa (n = 1,544)	rFVIIa (n = 506)
Head	22	33*
Face	6	7
Chest	25	33*
Abdomen	16	32*
Extremity	6	8

* Significantly different at $p < 0.005$.

TABLE 4. Demographic, Admission, and Laboratory Variables of Patients Not Treated and Treated With rFVIIa

Variable	No rFVIIa (n = 1,544)	rFVIIa (n = 506)
Age (yr)	24 (21–28; 1,534)	24 (21–28; 1,534)
ISS	17 (10–26; 1,542)	25* (17–34; 506)
GCS score	15 (13–15; 1,373)	14* (3–15; 468)
SBP (mm Hg)	118 (99–136; 1,387)	115* (86–133; 457)
DBP (mm Hg)	66 (52–79; 1,366)	62† (44–77; 449)
Heart rate (beats/min)	101 (81–122; 1,410)	112* (89–132; 470)
Temperature (°C)	98 (97.2–99.1; 857)	98 (97.1–99; 264)
BD (mmol/L)	4 (2–7; 888)	6* (3–12; 339)
INR	1.3 (1.1–1.5; 883)	1.4* (1.2–1.9; 333)
Hgb (g/dL)	12.3 (10.5–13.9; 1,164)	11.7† (10.0–13.4; 410)

Significantly different at * $p < 0.0001$ and at † $p < 0.005$.
Values are medians with the interquartile range and number of patients in parentheses.

TABLE 5. Use of Blood Components in Patients Not Treated and Treated With rFVIIa

Blood Component	No rFVIIa (n = 1,544)	rFVIIa (n = 506)
Sum PRBC (units)	5 (2–10; 1,544)	12* (6–21; 506)
Plasma (units)	2 (0–6; 1,544)	8* (4–14; 505)
Platelets	0.6 ± 1.74 (1,536)	0.9 ± 2.00† (506)
Cryoprecipitate	0.3 ± 1.12 (1,536)	0.5 ± 1.49† (506)
Massive transfusion (%)	27	66*

Significantly different at * $p < 0.0001$ and at † $p < 0.005$.
Values are medians with the 25% and 75% and number of patients in parentheses. Sum RBC is the product of the units of PRBC plus fresh whole blood. Mean values are presented for platelet and cryoprecipitate administration as the medians were 0 (0–0).

TABLE 6. Complication Rates for Patients Treated With and Without rFVIIa

Complication	No rFVIIa (n = 1,544)	rFVIIa (n = 506)
Deep vein thrombosis	6.1 (1,534)	10.9* (504)
Pulmonary embolism	4.9 (1,533)	6.6 (504)
Myocardial infarction	0.4 (1,535)	1.39† (504)
Stroke	0.7 (1,535)	1.2 (504)
Acute respiratory distress syndrome	4.4 (1,535)	7.3‡ (504)
Renal failure	2.9 (1,534)	7.5§ (504)
Mesenteric thrombosis	0 (1,533)	0 (503)
Overall complications	15 (1,539)	27§ (504)

Significantly different at * $p < 0.005$; † $p < 0.05$; ‡ $p < 0.01$; and § $p < 0.0001$.
Percentages are followed by the number of patients with data in parentheses.

regression, variables associated with mortality included higher ISS, HR, and transfusion of red blood cells and lower blood pressures (SBP and DBP), Hgb concentrations, and GCS score, as well as use of rFVIIa (Table 8). Using these variables, the calculated ROC was significant (area under the curve, 0.89; 95% CI 0.862–0.915). Use of rFVIIa was independently associated with death. Because use of the laboratory data limited the analysis to 633 patients, a secondary analysis was performed

TABLE 7. The Mortality Rate for the Overall Patient Population and After Propensity Analysis for Patient Treated or Not Treated With rFVIIa

Overall	6 h (%)	24 h (%)	30 d (%)	Overall (%)
No rFVIIa (n = 1544)	7.4	8.5	10.8	11.7
rFVIIa (n = 506)	10.9*	13.6*	22.3*	23.5*
Propensity matched				
No rFVIIa (n = 266)	6.8	9.4	13.5	14.3
rFVIIa (n = 266)	10.5	11.6	18.8	19.9

* Significantly different at $p < 0.01$.

TABLE 8. Multivariate Regression of Variables Associated With Overall Mortality

Variable	p	Odds Ratio	Lower 95% CI	Upper 95% CI
BD	0.000	1.097	1.064	1.129
INR	0.015	1.395	1.067	1.825
rFVIIa	0.022	1.672	1.079	2.593
ISS	0.000	1.045	1.027	1.062
GCS total	0.000	0.854	0.820	0.888
Constant	0.000	0.066		

with ISS, GCS score, SBP, and rFVIIa, allowing use of 1,387 patients (68% of the population). The ROC curve was significant (area under the curve, 0.88; 95% CI 0.859–0.907), and use of rFVIIa was still associated with mortality (OR = 1.668; 95% CI 1.181–2.356). Thus, injury severity, hypotension, and rFVIIa use were independent predictors of mortality and should be considered when matching populations.

Because clinical judgment was applied in the use of rFVIIa and this population was more severely injured and in shock, patients were matched based on propensity scoring using the following variables: ISS, GCS score, SBP, DBP, HR, and Hgb concentration. Some laboratory data were not used because they limited the patient population because of missing data. Of the 506 patients treated with rFVIIa, 235 (46%) were successfully matched. After matching, patients treated with rFVIIa received twice as many units of PRBCs (12 [6–21] units vs. 6 [3–11] units, $p < 0.0001$). Patients treated with rFVIIa also had an increased rate of massive transfusions (34% vs. 63%, $p < 0.0001$). Even with these differences, there was no difference in mortality (17% vs. 11%, $p = 0.111$); however, the incidence of complications increased with the use of rFVIIa (27% vs. 16%, $p = 0.005$). Because the number of units of PRBC transfused is associated with mortality and complications, it was subsequently included in the propensity score matching analysis. There were 266 (52%) of the patients treated with rFVIIa matched. There were no differences of any clinical consequence between those who received of rFVIIa and those who were not treated with the drug (Table 9). There were no significant differences in the rates of mortality (20% vs. 14%, $p = 0.08$; Table 7) or complications (21% vs. 21%, $p = 0.88$) between rFVIIa treatment and no treatment, respectively.

TABLE 9. After Propensity Matching Demographic, Admission, and Laboratory Variables of Patients Not Treated and Treated With rFVIIa

Variable	No rFVIIa (n = 266)	rFVIIa (n = 266)
Age (yr)	24 (21–28; 265)	24 (21–29; 266)
ISS	22 (14–30; 266)	25 (16–29; 266)
ISS >15 (%)	71	76
GCS score	15 (7–15; 266)	15 (4–15; 266)
SBP (mm Hg)	114 (93–136; 266)	115 (90–133; 266)
DBP (mm Hg)	64 (47–76; 266)	63 (47–76; 266)
Heart rate (beats per minute)	111 (89–131; 266)	110 (88–130; 266)
Temperature (°C)	98.0 (97.2–99.0; 179)	98.1 (97.3–99.1; 176)
BD	4 (2–8; 209)	5 (2–9; 210)
INR	1.3 (1.2–1.6; 208)	1.4 (1.1–1.8; 209)
Hgb (g/dL)	12 (10–13; 266)	12 (10–14; 266)
Sum PRBC (units)	10 (4–17; 266)	10 (6–16; 266)
Plasma (units)	5 (2–9; 266)	6* (3–10; 266)
Platelets	0 (0–1; 264)	0 (0–1; 266)
Cryoprecipitate	0 (0–0; 264)	0 (0–0; 266)
Massive transfusion (%)	53	51

* Significantly different, $p < 0.01$.
Values are medians with the interquartile range and number of patients in parentheses.

DISCUSSION

rFVIIa is one of the most studied Food and Drug Administration-approved drugs used off-label for the acute care of the patient who is bleeding.[21,22] In patients with traumatic injuries, there have been two randomized control trials and multiple single-center observational studies (Hauser et al., submitted for publication).[17,20] There is, presently, no prospective randomized evidence supporting a decreased mortality or an increase in thromboembolic events with rFVIIa use in patients with traumatic injuries. There are two small studies of combat casualties, which include both military and civilian patients requiring massive transfusions at a single combat support hospital, that suggest a reduction in blood transfusion requirements and 30-day mortality.[23,24] In this study of the effectiveness of the use of rFVIIa in US military casualties, we found no difference in mortality in a population of patients matched by propensity score.

The rate of complications, specifically those associated with thromboembolic events, has also been a focus point of studies related to the safety of rFVIIa, suggesting a high rate of thromboembolic adverse events after use of rFVIIa; however, comparative populations are not presented.[28,29] In review of the randomized control trials of various patient populations, the conclusion is that there is no evidence to support an increased complication rate.[21,22] A review of studies of rFVIIa use in patients with traumatic injuries found no definitive evidence to support a difference in thromboembolic events (Hauser et al., submitted for publication).[20,24] In this study in the overall population, complications increased with administration of rFVIIa, but when adjusted for increased injury severity, there were no differences.

Horton et al.[15] reported that rFVIIa use in major trauma centers in the United States was related to the volume of trauma patients. The more patients a center treated, the greater the use of

rFVIIa. The percentage of trauma admissions using rFVIIa ranged from 0.3% to 1% of admissions. During the period of this study, there were 18,638 records of US military casualties in the JTTR. With this number as the denominator, the rate of use in the military population was 2.7% (511 of 18,638). This rate was notably higher than the rate reported for major civilian centers. This difference may be because of the greater rate of major bleeding in combat casualties, usually reported at two to three times than that in civilian studies. The rate of massive transfusions in patients requiring a transfusion is 11% in the civilian population and 36% in this study of combat casualties.[30] The rate of coagulopathy in combat casualties also increased compared with that of civilian patients. The incidence of coagulopathy (international normalization ratio >1.5) in this study of combat casualties was 35% in contrast to 25% to 28% reported for civilian populations.[7–9] In addition, the use of rFVIIa in the military population may have been associated with limited access to blood components, specifically platelets and cryoprecipitate.[18] Thus, the higher rate of use of rFVIIa in the combat casualties seems justified.

In this observational study of the use of rFVIIa in military care facilities during overseas contingency operations, it seems that the physicians selected patients for administration of rFVIIa based on criteria other than those put forth in the clinical practice guideline. Although there are a greater percentage of patients meeting one of the guideline criteria who were treated with rFVIIa, there were more patients (397 vs. 1,072) who met one of the criteria who were not treated. Sixty-nine percent of those patients not treated had one or more criteria positive. Furthermore, more patients received a massive transfusion in the no treatment group (414 vs. 332), suggesting a strong influence of the provider in making a decision to use rFVIIa, based on influencing factors other than the guideline. This is apparent in the initial attempt at propensity score matching, where a marked increase was noted in the use of PRBC in patients treated with rFVIIa. This difference implies that clinicians administered rFVIIa based on bleeding irrespective of physiologic or laboratory data. It also points out the difficulty in differentiating bleeding amenable to treatment with rFVIIa from that requiring surgical intervention. Thus, selection based on bleeding would seem to be a major confounding factor. In the final analysis, taking PRBC transfusion into account, a selection bias is also noted in comparison of the overall analysis with the propensity analysis. There was a reduction in seriousness of injury of patients receiving rFVIIa in the population matched by propensity analysis because the amount of blood components used and the rate of massive transfusions were reduced compared with the overall rFVIIa population. Therefore, those patients requiring the greatest amount of blood components were not able to be matched. The process used by physicians to use select rFVIIa seems to have contributed to the association of rFVIIa with mortality on multifactorial logistic regression because military clinicians were giving rFVIIa to most severely injured patients with major bleeding.

Stein et al.[31] have raised the issue of rFVIIa's use when patients are in extremis and administration of rFVIIa is futile. In this study, patients receiving rFVIIa had a higher ISS and greater incidence of massive transfusion, both of which are associated with poorer outcomes. Furthermore, Stein et al. noted that patients with profound acidosis and hypovolemia predicted failure of rFVIIa. In this study, patients administered rFVIIa at admission had greater base deficit, lower blood pressures, and increased HRs indicative of worse hemorrhagic shock. All of these factors further suggest physician bias based on clinical judgment for use of rFVIIa in the more severely injured bleeding patients.

Observational nonrandomized studies have a role when randomized control trials are not available or feasible as is the case in the combat environment. As expected with an observational study, the present data demonstrated striking differences between treated and untreated patients associated with a major disparity in the severity of injury attributed to physician selection bias. The goal of a propensity analysis is to use observational data to create an analysis that resembles what would have occurred under the optimal conditions of a randomized control trial.[32] We used propensity score matching to compensate for the difference in injury severity. As noted above, this eliminated the more severely injured patients from the treated population and the less-injured patients from the population not treated. Matching using ISS, GCS score, SBP, DBP, HR, Hgb, and sum PRBC administered as indices of injury severity and shock state accomplished the goal of creating uniform populations. There were no clinically significant differences between groups in a wide range of variables after the matching (Table 9). After matching, there was no significant difference in mortality or complication rates between treated and untreated patients. However, the trend ($p = 0.08$) of an increased mortality with rFVIIa should be considered, especially in light of its being independently associated with mortality in a multivariate logistic regression. This difference may again be the result of rFVIIa's being used as a last-ditch effort in massively bleeding patients, as mentioned above, or other unmeasured clinical factors. At present, existing data do not support the empiric use of rFVIIa use in combat casualties. To fully understand the use of rFVIIa, funding agencies must undertake studies validating predictive algorithms that identify patients who could potentially benefit from this drug and other drugs. This must be accomplished before efficacy studies can be undertaken.

Limitations of this study should be noted. This was an observational study with inherent limitations, specifically a lack of randomization of patient assignment, which we attempted to handle by performing a propensity analysis. Another limitation is the lack of information on the time of administration and dose of rFVIIa used. Previous work in combat casualties suggests that administration of rFVIIa early in the course of care is of benefit, whereas other researchers have also demonstrated that administration late as a last-ditch effort is futile.[23,24,31,33] In addition to the improved survival with early rFVIIa use, there was also an increased use of fresh whole blood and cryoprecipitate in the rFVIIa group. The relationship of rFVIIa use with products containing fresh fibrinogen needs to be further investigated. The lack of information in this study on time of administration and the status of the patient at that point is of concern. The recommended dose in the military clinical practice guideline is 90 μg/kg to 120 μg/kg IV push. We do not know whether this dose was used in this study; however, an earlier study in a

combat support hospital found the dose of rFVIIa to be 105 μg/kg to 110 μg/kg, supporting adherence to the guideline.[23]

As the military introduces new and novel devices, drugs and clinical practice guidelines into the care of the combat casualties, it is incumbent to evaluate their effectiveness and safety. This study is such an attempt. Efforts have also been undertaken to evaluate the use of tourniquets, initial burn care resuscitation during evacuation, plasma:platelet:PRBC ratios, and use of fresh whole blood.[5,18,34–37] These efforts are facilitated by the presence of the JTTR and the in-theater research team.[26] This form of vigilance must continue to be supported, and we must adhere to the highest standards of clinical research within the limitations of the combat environment, or through support of research in civilian institutions.

In military casualties, rFVIIa is used in the most severely injured patients based on physician selection rather than rigid adherence to published guideline criteria. Use of rFVIIa is not associated with an improvement in survival or an increase in complications. The undetected bias of physician selection of patients for treatment with rFVIIa, likely, has an impact on case matching to achieve equivalence similar to that of randomized control studies. This inability to match populations, thus, prevents definitive interpretation of this study and other studies of similar design. This problem emphasizes the need to develop entry criteria to identify patients who would potentially benefit rFVIIa and the need to subsequently perform efficacy studies.

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DISCUSSION

Dr. J. Wayne Meredith (Winston-Salem, North Carolina): Thank you, David, and I thank the association for the privilege of discussing this excellent paper.

I want to thank the authors for a well-written and a candid evaluation of Activated Factor VII in massive transfusion in combat casualty in patients.

This is a pretty heroic, courageous paper to do. You didn't mention it but you may recall a significant buzz in the lay press condemning our military for the use of Recombinant Factor VII in our injured warriors.

And to then undertake the process of saying we're going to objectively look at the work we've done and the patients we treated and how that came out in the face of having faced that scrutiny, I strongly applaud your integrity and your courage for approaching it this way.

Now, to finish, to look at the study a bit, many people aren't familiar with this propensity analysis but it is a valid, logical way to try to salvage something from data where you have no control groups and, therefore, can't directly test a hypothesis.

And I think it is worthwhile to walk out of here saying that based on a very rigorous, valid statistical model we have not hurt our soldiers by using Factor VIIa. And I think that's important and I think it's worth people knowing and I think we should all leave here with that.

Having said that, there are some other problems that you've elaborated and which Doctor Knudson talked about in her paper yesterday. Sixty-nine percent of the patients that were candidates to get the drug didn't get the drug, which makes it hard to interpret this study.

It's an ill-defined selection criterion between who gets it. And the guidelines, if you read them carefully – you mentioned it Doctor Wade but didn't emphasize it – did not say these are the patients who should get Recombinant Factor VIIa and these are the patients who should not.

The guidelines say it should be considered in patients with massive transfusion requirements. Those guidelines are probably too loose to form the basis of a rigorous study.

So really my questions for you are – and I think the time to decide, there are enough data I think to say does it work or does it not work, is it worth it or is it not worth it and is it time to say let's don't use this drug or let's only use it on a controlled trial, in a controlled circumstance.

I would say in the military that controlled circumstance needs to be based on defined criteria where we're going to use it and use it all the time and these are the criteria where we're going to stop using it – when it's too late, when we're desperate, when we've just given 35 units of blood.

And I think one of those two things probably is the right thing to do and so I would ask the question, what is next for you? Are you going to change the guidelines? Are you going to discontinue its use?

I think you've proven that it's probably not helpful to continue to use it on an ad hoc, clinician judgment basis.

Dr. Charles E. Wade (Fort Sam Houston, Texas): I would like to thank Doctor Meredith for his comments.

There is a difference between a policy and a clinical practice guideline in the military. The clinical practice guidelines are a guideline. They are not a substitute for clinical judgment. And so when we put these guidelines out they are to provide input to help a physician make a decision. They are not a policy; therefore, they are not enforced. I just wanted to make that clear. So I don't think that there is going to be a policy.

We try to use the best clinical data that's available to support putting these guidelines out. So many of you are contributors to our formulation of these particular guidelines.

Most of us believe that there is a population that could benefit. The question is defining that population a priori. And I think we're going to put more work behind that and be able to narrow down the patients that need this particular product.

Dr. Charles E. Lucas (Detroit, Michigan): Two brief questions. Is my military continuing to resuscitate my injured citizens with the colloid Hextend which Doctor Holcomb showed last year to be conclusively coagulopathic? That would affect how many pro-coagulants you have to give to both groups to achieve hemostasis?

Secondly, with your objective to restore the ideal amount of pro-coagulants in any of these patients in either group did you actually measure the pro-coagulant levels, particularly Factor VII level, in order that all of us could help learn the ideal plasma to red cell ratio by science rather than by some gestalt?

Dr. Slate Wilson (Portland, Oregon): I have to lower the microphone here, even though we're the same age. So, Slate Wilson, Portland, Oregon.

I noticed that the, that fresh warm blood, presumably warm blood, was used in many of these cases and that's only available in the military as far as I know.

My question is, would the use of fresh warm blood have confounded some of your studies in that both were probably used in the same patient?

Dr. Charles E. Wade (Fort Sam Houston, Texas): First for Doctor Lucas, Doctor Holcomb's presentation last year on Hextend and coagulopathy was a model in which they received more than that would be administered to a human by the limits.

It was, I think it was the equivalent of 1,500 mls which would put them above what we presently use in theater. Most of the medics are only carrying two 500 ml bags. So I don't believe that's a contributing factor.

As to the issue of pro-coagulants, we have been working for the last three years trying to get blood samples out of Baghdad. I must say that FedEx, DHL and the Air Force have not been successful.

So to actually – we've drawn them but they have not arrived here frozen because they get stuck by the State Department, USDA and other fun agencies to play with so unfortunately we don't have that data.

But we have been trying very diligently to do that. And I must commend there are numbers of people in the audience who have been serving as part of the research team in theater helping us trying to get those samples.

As for Doctor Wilson, yes, both groups received fresh whole blood. And it was a greater prevalence the use of fresh whole blood in the group that received Factor VII in that group.

As we reported yesterday in patients that receive Factor VII, fresh whole blood there appears to be a survival advantage, once again, when the groups are matched to appropriate injury severities.